PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2004/012156	18.08.2004	19.08.2003

International Patent Classification (IPC) or both national classification and IPC
C07C269/06, C07D263/26, C07C271/64

Applicant
TAKASAGO INTERNATIONAL CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2004/012156

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-4,6

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-4,6

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	5
Inventive step (IS)	Yes:	Claims	
	No:	Claims	5
Industrial applicability (IA)	Yes:	Claims	5
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1) Reference is made to the following documents:

D1: WEI ZHUANG ET AL.: "Catalytic enantionselective addition of aromatic amines to enones: synthesis of optically active beta-amino acid derivatives" CHEMICAL COMMUNICATIONS, no. 12, 2001, pages 1240-1241, XP002317996

D2: LUCA FADINI AND ANTONIO TOGNI: "Ni(II) Complexes containing chiral tridentate phosphines as new catalysts for the hydroamination of activated olefins" CHEMICAL COMMUNICATIONS, no. 1, 2003, pages 30-31, XP002317997

D3: KELIN LI ET AL.: "Air- and moisture-stable cationic (diphosphine)palladium(II) complexes as hydroamination catalystsl X-ray crystal structures of two [(diphosphine)Pd(NCMe)(OH2)]2+[OTf]2- complexes" JOURNAL OF ORGANOMETALLIC CHEMISTRY, vol. 665, 2003, pages 250-257, XP002317998

D4: KELIN LI AND KING KUOK (MIMI) HII: "Dicationic [(BINAP)Pd(solvent)2]2+[TfO-]2:enantiosele ctive hydroamination catalyst for alkenoyl-N-oxazolidinones" CHEMICAL COMMUNICATIONS, no. 10, 2003, pages 1132-1133, XP002317999

D5: YOSHITAKA HAMASHIMA ET AL.: "Amine-salt-controlled, catalytic asymmetric conjgate addition of various amines and asymmetric protonation" ORGANIC LETTERS, vol. 6, no. 11, 27 May 2004 (2004-05-27), pages 1861-1864, XP002318000

2) The present application relates to a process for producing an optically active β-amino acid derivative, which comprises reacting an α,β-unsaturated carboxylic acid derivative with an amine or a salt thereof, in the presence of a chiral catalyst. It further relates to the particular β-amino acid compounds of formula (4b) as mentioned in Claim 6.

3) Re Item III

Asymmetric conjugated additions of amines to α,β-unsaturated carboxylic acid derivatives, wherein asymmetry is induced by the presence of a chiral catalyst, are well-known in the art. This resulted in that the initial phase of the search revealed such a large number of documents relevant to the issue of novelty, that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For this reason, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has been restricted to the process for

producing optically active β-amino acid derivatives of formula (4a) disclosed in Claim 5 (it is to be noted that a search of only the compounds of Claim 6 also results in an overflow of documents).

Accordingly, **the following substantive examination relates only to the subject-matter for which a complete search has been carried out, namely the subject-matter of Claim 5.**

4) Re Item V

4.1 Novelty (Art. 33(2) PCT)

D1 discloses (cf. abstract, Equation 2 and tables 1 and 2) a catalytic enantioselective addition of aromatic amines to α,β-unsaturated acid derivatives (*N*-alkenoyl oxazolidinones) in the presence of chiral catalysts (transition metal complexes).

D2 describes in Scheme 1 the addition of anilines to α,β-unsaturated nitriles or carboxylic acid derivatives (EWG= CN or COOR) in the presence of 1-5 mol% catalyst, wherein the catalyst is a Ni(II) complex containing chiral tridentate ferrocenyl phosphines (cf. abstract).

D3 evaluates in Table 2 the addition of amines to substituted acrylate, crotonate, and cinnamate, in the presence of 2 mol% chiral catalyst. Entry 11 particularly shows addition of aniline to methyl acrylate.

D4 relates (cf. abstract, Scheme 2, and Table 1) to enantioselective hydroamination catalysts for *N*-alkenoyl oxazolidinones. In particular the document studies the enantioselective addition of anilines to *N*-alkenoyl oxazolidinones.

In the light of any of **D1-D4**, the subject-matter of Claim 5 may not be regarded as novel.

4.2 Inventive Step (Art. 33(3) PCT)

Inventive step cannot be acknowledged for Claim 5 since no difference exists between its subject-matter and the prior art. Nevertheless, the attention of the Applicant is drawn to the fact that, if he is able to provide a set of claims which is novel over the prior art, an inventive step will be acknowledged only for a scope of claim for which it is credible that the expected effects may be expected. The present definition of the claim, wherein the

different groups R may be substituted by any possible radical, does not appear to fulfil this requirement. Neither does a definition, wherein essential features are lacking (cf. point 6 below).

4.3 Industrial applicability (Art. 33(4) PCT)

Is acknowledged for Claim 5.

5) Re Item VI

The priority document pertaining to the present application was not available at the time of establishing this written opinion. Hence, it is based on the assumption that Claim 5 enjoys priority rights from the filing date of the priority document (19.08.2003). If it later turns out that this is not correct, the document **D5**, indicated in the International Report as "P", could become relevant to assess whether Claim 5 satisfies the criteria set forth in Article 33(1) PCT.

6) Re Item VIII

Claim 5 lacks clarity (Article 6 PCT) for several reasons:

- The nature of the chiral catalyst present in the claimed process is regarded as an essential feature if an enantiomeric excess is intended to be obtained. This should therefore be specified in the definition of the claim.

- It is not clear what the Applicant means by "producing an optically active β-amino acid derivative". When reading the description and looking at the examples, it seems that he refers to the production of optically active enantiomeric mixtures, i.e. mixtures of enantiomers, which are enriched in one of said enantiomers. However, this is not what the claims define, since they relate to the production of optically active derivatives, and such derivatives are obtained even if the resulting product is optically inactive, i.e. a racemate.

- The asterisks in formulae (2) or (4a) indicate that the carbons α and β are both asymmetric. However, if R^3 is hydrogen the α-carbon is not asymmetric, and if $R^1 = R^2$, the β-carbon is not asymmetric. As these two possibilities are encompassed in the definition of R^1-R^3, the formulae appear to be inconsistent.

- Formula (I) is defined as a α,β-unsaturated carboxylic acid derivative, but R^4 may be a heterocyclic group, which is not necessary linked to the acyl moiety by a heteroatom of the cycle. This introduces ambiguity, since Formula (I) would thus encompass as carboxylic acid derivatives compounds which are actually ketones.